The Prognostic Value of Syncope on Mortality in Patients With Pulmonary Embolism: A Systematic Review and Meta-analysis

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Study objective: Syncope is a presenting symptom in 10% to 20% of patients with pulmonary embolism. We perform a meta-analysis to clarify the prognostic value of syncope on short-term mortality in pulmonary embolism patients and its association with hemodynamic instability.

Methods: PubMed, EMBASE, and the Cochrane Library were searched up until January 7, 2020. Studies reporting inhospital or 30-day mortality of adults with pulmonary embolism with and without syncope were included. Quality of included studies was evaluated with the Quality in Prognosis Studies tool. Meta-analysis was conducted to derive pooled odds ratios (ORs) and risk differences for the relation of syncope with mortality and hemodynamic instability. To study the influence of hemodynamic instability on the association between syncope and mortality, meta-regression was performed.

Results: Search and selection resulted in 26 studies, of which 20 were pooled, involving 9,419 of 335,120 patients (3%) with syncope. Syncope was associated with higher mortality (OR 1.82; 95% confidence interval [CI] 1.14 to 2.90; I^2 88%; risk difference 4% [95% CI 1% to 8%]) and higher prevalence of hemodynamic instability (OR 4.36; 95% CI 2.27 to 8.37; I^2 93%; risk difference 12% [95% CI 7% to 18%]). OR for mortality in patients with pulmonary embolism with syncope versus without it was higher in the presence of a larger difference in hemodynamic instability between groups (coefficient 0.05; 95% CI 0.01 to 0.09).

Conclusion: The association between syncope and short-term mortality in patients with pulmonary embolism is explained by a difference in hemodynamic instability. This emphasizes the importance of risk stratification by hemodynamic status in pulmonary embolism patients with and without syncope. [Ann Emerg Med. 2020;76:527-541.]

Please see page 528 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Pulmonary embolism is a common disease, affecting 1 in 1,000 persons annually.[1] The recent Pulmonary Embolism in Syncope Italian Trial has shown that 1 in 6 patients admitted to the hospital with syncope has pulmonary embolism.[2] Although these results have been contradicted by multiple studies, it has drawn attention to syncope in relation to pulmonary embolism.[3,4]

Syncope is a symptom of pulmonary embolism in 10% to 20% of patients.[5-7] Because syncope often results from transient hypotension, in clinical practice the question of whether it reflects high-risk pulmonary embolism is frequently raised. High-risk pulmonary embolism is defined as pulmonary embolism in the presence of hemodynamic instability: cardiac arrest, obstructive shock, or persistent hypotension (systolic blood pressure $\leq$90 mm Hg or a decrease of 40 mm Hg in systolic blood pressure for >15 minutes, not caused by arrhythmias, hypovolemia, or sepsis).[8] In these patients, mortality is as high as 30% if left untreated.[9] Therefore, timely recognition and adequate treatment are of vital importance. Systemic thrombolysis is currently the first choice of treatment.[8] Although effective in reducing pulmonary embolism–related death, it comes at the cost of a 9% to 22% risk of major bleeding, including intracranial bleeding.[10,11] Clearly, understanding the clinical relevance of syncope related to hemodynamic instability and mortality in pulmonary embolism patients is paramount to guide proper patient selection for systemic thrombolysis or other reperfusion strategies. Similarly, adequate risk stratification in patients with pulmonary embolism is essential to determine the need for hospital admission with or without hemodynamic monitoring. Syncope is not yet included in commonly used tools.[12-14]

Editor's Capsule Summary

What is already known on this topic

Syncope can be a presenting feature of pulmonary embolism and is known to be associated with an increased risk of death.

What question this study addressed

Is the increased risk of death associated with syncope explained by the presence of hemodynamic instability?

What this study adds to our knowledge

Meta-regression of 20 studies showed that the mortality risk associated with syncope increased significantly as the proportion of hemodynamically unstable patients increased, indicating that the association between mortality and syncope is explained by hemodynamic instability.

How this is relevant to clinical practice

Syncope need only be considered an adverse prognostic symptom if it is associated with hemodynamic instability.

Because it is relatively easy to identify and does not require continuous monitoring, it may be an attractive addition to current risk-assessment strategies.

Importance

A previous meta-analysis of studies on the prognostic value of syncope in patients with pulmonary embolism found that those who presented with syncope were at increased risk of mortality and hemodynamic instability.[15] However, when the analysis was restricted to normotensive patients, no difference in mortality was found. The authors proposed 2 possible explanations. First, hemodynamic instability may be the main predictor of early mortality rather than syncope. Second, because the association between syncope and early mortality was more pronounced in studies with a lower score at formal quality assessment, these results may be biased.

In the present study, we aimed to overcome and clarify aforementioned issues by using meta-regression analysis and including additional recently published relevant articles. Meta-regression is a more flexible, efficient, and powerful approach to explore heterogeneity compared with subgroup analysis.[16] Because the effect of covariates on the effect estimate can be assessed on a continuous scale (eg, proportion of patients with hemodynamic instability), data of all included studies can be used. With meta-regression as well as a larger number of relevant studies, we may more precisely determine a possible association between syncope and mortality in patients with pulmonary embolism.

Goals of This Investigation

We sought to evaluate the prognostic value of syncope on short-term (inhospital or 30-day) mortality in patients with pulmonary embolism and clarify the potential association between syncope, hemodynamic instability, and short-term mortality.

MATERIALS AND METHODS

Study Design

We conducted a systematic review, meta-analysis, and meta-regression analysis. A review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero) before conduct of this review. Methods and results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[17]

A systematic search in PubMed, EMBASE, and Cochrane Library databases was performed on April 25, 2018, and updated up to January 7, 2020. Search terms included were "pulmonary embolism" AND "syncope" AND "mortality" OR "outcome" and synonyms. The search in PubMed is shown in Appendix E1, available online at http://www.annemergmed.com.

Reference lists and citation lists of the included articles were searched manually to be as inclusive as possible. ClinicalTrials.gov and PROSPERO were searched for unpublished trials and systematic reviews. All identified publications and abstracts were screened by 2 researchers (M.A.d.W. and E.D.P.v.B.) independently. Studies were included if they included patients (≥18 years) with pulmonary embolism, reported on syncope as a prognostic parameter, and reported data on inhospital or 30-day mortality for all patients with and without syncope separately. Case reports, case series, narrative reviews, and articles in languages other than English, German, or Dutch were excluded. Any disagreement was resolved by consensus with a third researcher (M.N.). Data were extracted from full-text articles only because abstracts yielded insufficient information in regard to our research question.

Data Collection and Processing

Data extraction was carried out by one researcher independently (M.A.d.W.) and verified by another (E.D.P.v.B.), according to standardized forms. Disagreement was solved by a third researcher (M.N.). If

required data were unavailable, authors were contacted by e-mail. Extracted information included general study information, demographics, comorbidities, predisposing factors for pulmonary embolism, hemodynamic status and signs and symptoms at presentation, laboratory or radiographic abnormalities, hemodynamic instability, pulmonary embolism treatment, and short-term mortality.

Quality of the included studies was evaluated at the study level by one researcher (M.A.d.W.) and verified by another (E.D.P.v.B.) with the Quality in Prognosis Studies (QUIPS) tool.[18] The tool comprises 7 domains: study participation, study attrition, prognostic factor measurement, outcome measurement (assessed for both mortality and risk-classification outcomes), study confounding, statistical analysis, and statistical reporting. Risk of bias in the scope of each domain was rated as low, high, or unclear. To be able to perform sensitivity analyses with the omission of studies at a high risk of bias, we assigned points per QUIPS domain to each of the studies. Two points were assigned for high risk of bias; one point for unclear risk of bias. Total scores were used to identify quartiles. In case of insufficient information about QUIPS domains, authors were contacted. To examine the presence of reporting bias (eg, selective reporting of positive findings), PubMed, ClinicalTrials.gov, and the Dutch Trial Registry were searched for prepublished protocols published to compare the outcomes planned to study with those reported. If unavailable, outcomes reported in the results section were compared with those mentioned in the methods section.

Outcome Measures

The primary outcome was short-term mortality, defined as death during hospital admission for pulmonary embolism or within 30 days of pulmonary embolism diagnosis. The secondary outcome was hemodynamic instability, which was considered "massive" or "high-risk" pulmonary embolism according to American Heart Association or European Society of Cardiology guidelines, or, if unavailable, hypotension (systolic blood pressure <90 or <100 mm Hg, depending on availability), preferably for greater than 15 minutes.[8,19] Presyncope was defined as a state resembling the prodrome of syncope without being followed by loss of consciousness.[5] Syncope was defined as a transient loss of consciousness because of cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.[5]

Primary Data Analysis

To provide an overall estimate of the effect of syncope on short-term mortality and hemodynamic instability, odds ratios (ORs) and absolute risk differences from individual studies were pooled. A random-effects model was applied to derive pooled ORs and absolute risk differences with 95% confidence intervals (CIs) because heterogeneity in regard to sample characteristics and methods between studies was assumed to be present.[20] Results were graphically presented in forest plots. Statistical heterogeneity was tested by visual inspection of forest plots, as well as by using Cochran's Q test and Higgins's I^2 test statistic. The latter indicates the proportion of variance between studies that may be explained by heterogeneity instead of chance.[21] Values of 25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively.[21] Studies assessing presyncope and syncope separately were included in pooled analyses only if data of patients with syncope could be analyzed separately from those with presyncope and without syncope.

Prespecified sensitivity analyses were conducted by dividing studies into groups based on relevant study characteristics to assess whether these may influence effect estimates.

To estimate the presence of publication bias (ie, selective reporting of positive findings), funnel plots of the OR for mortality against corresponding standard errors were created and visually inspected to determine whether deviations of symmetry occurred. In addition, Egger's regression test was performed to test for asymmetry because the number of included studies and variation in sample size were sufficiently large.[22]

To investigate whether the OR of mortality for patients with versus without syncope could be explained by the difference in hemodynamic instability or other characteristics, meta-regression was performed. In meta-regression, similar to normal regression analysis, the effect estimate is predicted according to the value of one or more explanatory variables, although in meta-regression it is assessed at the study level rather than at the individual patient level.[23] A DerSimonian-Laird random-effects model, the most widely used model to assess between studies variance, was used with OR of mortality for patients with syncope versus without it as outcome.[24] Univariate analyses were performed with absolute differences (percentage) between patients with and without syncope in the presence of hemodynamic instability, cardiac disease, malignancy, and use of thrombolytic therapy, and with standardized mean difference in age as covariate. The standardized mean difference in age in individual studies was used to adjust for differences in mean age between studies, and was calculated by dividing the difference in mean age between patients with and without syncope by the standard deviation. R-statistic programming (metafor package; version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria) was used for meta-analysis statistics.[20]

RESULTS

Characteristics of Study Subjects

Titles and abstracts of 1,858 potentially eligible studies were screened, resulting in 26 studies that met our inclusion criteria (Figure 1).[7,25-49] No relevant ongoing trials or systematic reviews were identified. Four studies were not included in the final analysis because part of the study population was already included in another study with a larger total study population[7,34,41,45] or a less selective sample,[44,49] or in an individual patient analysis.[42,46] Characteristics of the included studies are presented in Table 1. A total of 355,120 patients with pulmonary embolism were included in the meta-analysis, of whom 9,419 (3%) had syncope.

Data on short-term mortality in all patients with and without syncope separately were available in 20 studies.[25-34,36-40,42-44,47,48] The other 2 studies could not be pooled: one study did not report outcomes of patients with syncope separate from those with presyncope, whereas another study reported only adverse 30-day outcome.[35,41] Overall, 30-day or inhospital mortality was 13% (95% CI 13% to 14%) in patients with syncope (1,207/1,949) and 15% (95% CI 14% to 15%) in patients without it (50,883/345,971). The included studies were contradictory in regard to the association between syncope and short-term mortality (Figure 2*A*): ORs in univariate analyses ranged from 0.44 (95% CI 0.06 to 3.35) to 13.10 (95% CI 0.52 to 327.65). The pooled OR of 1.82 (95% CI 1.14 to 2.90; I^2 88%; Cochran's Q test P=.01) for patients with pulmonary embolism with syncope versus those with pulmonary embolism without syncope indicated a positive association of syncope with short-term mortality in patients with pulmonary embolism. This corresponded to a weighted absolute risk difference of 4% (95% CI 1% to 8%), indicating a higher risk of mortality in patients with syncope (Figure 2*B*). The majority of the included patients (97%) originated from one large nationwide retrospective

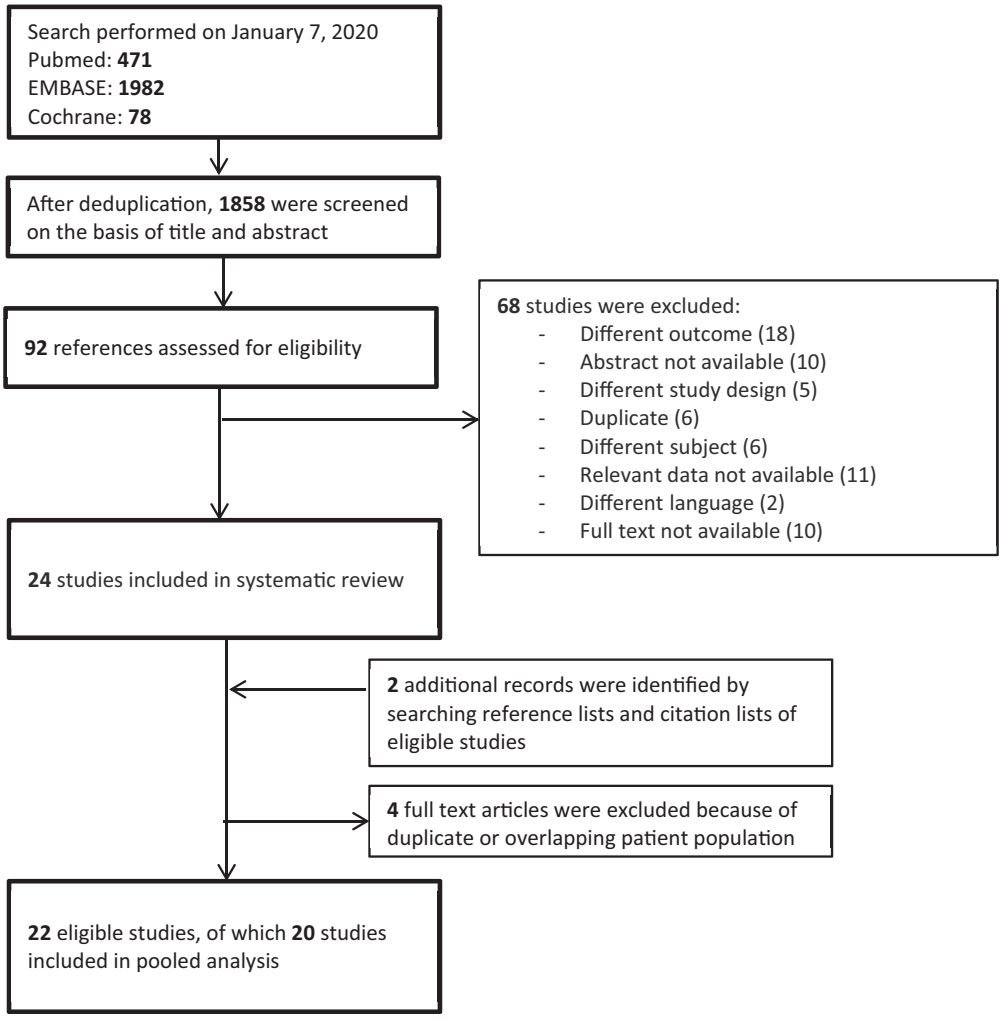


Figure 1. Flow diagram for study selection.

Table 1. General characteristics of the included studies.

Author	Year	Design	Population	n	Syncope (%)	Age (Mean [SD] or Median [IQR])	Women, %	Mortality	Risk Classification	HD Unstable (%)
Studies on prognostic value of syncope in patients with PE										
Mohebali[25]	2019	Retrospective	H*	477	41 (9)	63 (16)	53	30-day	Similar to ESC	8
Natanzon[26]	2019	Retrospective	C	212	40 (19)	65 (16)	56	Inhospital	Similar to ESC	0
Ploesteanu[27]	2019	Retrospective	H	79	11 (14)	69 (14)	65	Inhospital	SBP <90 mm Hg	13
Keller[28]	2018	Retrospective	H	345,889	7,936 (2)	S: 75.0 (62.0–82.0); 76.0 (68.0–83.0) NS: 73 (61.0–80.0); 72.0 (60.0–80.0)†	53	Inhospital	Hemodynamically unstable‡	15
Roncon[29]	2018	Prospective	ED, C, I	1,716	219 (13)	70 (15)	57	30-day	ESC	9
Lee[30]	2018	Retrospective	H	1,084	45 (4)	S: 68 (54–73) NS: 69 (60–76)	57	Inhospital	ESC	4
Omar[31]	2018	Retrospective	H	552	68 (23)	54 (17)	53	Inhospital	AHA	4
Ozyurt[32]	2017	Retrospective	H	322	16 (5)	73 (61–84)	59	30-day	ESC	0§
Iqbal[33]	2017	Retrospective	ED	219	15 (7)	64 (15)	45	30-day	"Hypotension"	9
Seyyedi[34]	2016	Prospective	ED	351	39 (11)	60 (17)	45	30-day	SBP <90 mm Hg	1
Keller[35]	2016	Retrospective	I	182	20 (11)‖	69 (15)	62	Inhospital	ESC/AHA	4
Altinsoy[47]	2016	Retrospective	P	179	23 (13)	68 (22–96)	51	Inhospital	SBP <90 mm Hg	2
Duplyakov[36]	2014	Retrospective	H¶	117	35 (30)	52 (13)	47	Inhospital	ESC	32
Calvo-Romero[37]	2004	Retrospective	I	154	14 (9)	S: 75 (7) NS: 68 (13)	62	Inhospital	SBP <100 mm Hg	8
Castelli[38]	2003	Prospective	ED	70	10 (14)	S: 70 (11) NS: 71 (14)	44	Inhospital	Similar to ESC	0
Studies on risk assessment strategies or predictors of prognosis in PE with data available on syncope and mortality										
Kochmareva[39]	2018	Prospective	H¶	136	34 (25)	67 (16)	63	30-day	ESC	21
Ishimaru[40]	2018	Retrospective	ED	52	12 (23)	66 (14)	60	30-day	ESC	20
Hobohm[41]	2016	Prospective	H	388	50 (13)	70.5 (54–77)	54	30-day#	Similar to ESC	0
Zengin[48]	2015	Retrospective	ED**	139	8 (6)	73 (6)	63	30-day	SBP <100 mm Hg	7
Bova[42]	2014	IPDMA, prospective	H	2,874	249 (12)	72 (60–80)	61	30-day	SBP <100 mm Hg	6
Agrawal[43]	2014	Prospective	C	200	28 (14)	49	40	Inhospital	n.a.	n.a.
Geibel[44]	2005	Prospective	H¶	508	206 (41)	63 (15)	58	30-day	ESC	100

Table 1. Continued.

Author	Year	Design	Population	n	Syncope (%)	Age (Mean [SD] or Median [IQR])	Women, %	Mortality	Risk Classification	HD Unstable (%)
Duplicate or overlapping patient population										
Jenab[7]	2015	Prospective	ED	335	36 (11)	60 (17)	44	In-hospital	SBP <90 mm Hg	3
Jiménez[46]	2014	Prospective	ED	848	128 (15)	72 (59–80)	51	30-day[††]	Similar to ESC	0
Lankeit[45]	2012	Prospective	H	136	30 (22)	68 (56–76)	60	30-day[#]	Similar to ESC	0
Konstantinides[49]	1997	Prospective	H[¶]	719	180 (25)	63 (15)	60	30-day	ESC	43

IQR, Interquartile range; *HD*, hemodynamically; *PE*, pulmonary embolism; *H*, all patients in the hospital or unspecified; *ESC*, European Society of Cardiology; *C*, cardiology department; *SBP*, systolic blood pressure; *I*, internal medicine department; *AHA*, American Heart Association; *P*, pulmonary department; *IPDMA*, individual patient data meta-analysis.

*Only hospitalized patients who underwent transthoracic echocardiography.

†Reported medians and interquartile ranges indicate patients with syncope who are hemodynamically stable and unstable, and patients without syncope who are hemodynamically stable and unstable, respectively.

‡Hemodynamically stable pulmonary embolism was defined as patients with pulmonary embolism without shock (*ICD* code R57), mechanical ventilation (not including mechanical ventilation during surgery; Operation and Procedure Code codes 8-70 and 8-71), and cardiopulmonary resuscitation (OPS code 8-77) during hospital stay.

§Patients with hypotension and previous syncope were excluded.

‖Including syncope and presyncope.

¶Intermediate- and high-risk patients only.

#Included in adverse 30-day outcome, defined as death from any cause, or at least 1 of the following: (1) need for intravenous catecholamine administration (except for dopamine at <5 μg/kg per minute) to maintain adequate tissue perfusion and prevent cardiogenic shock, intubation, or cardiopulmonary resuscitation.

**Elderly patients only (>65 years).

††Included in adverse 30-day outcome, defined as death from any cause, hemodynamic collapse, or adjudicated recurrent pulmonary embolism.

cohort study, which was thus an important driver of the results.[28] Therefore, we performed a sensitivity analysis with the omission of this study. In this analysis, 9,234 patients were included, of whom 1,213 (13%) had syncope. Short-term mortality was 18% in patients with pulmonary embolism and syncope and 8% in those with pulmonary embolism without syncope, corresponding to an OR for mortality of 1.95 (95% CI 1.30 to 2.93; I^2 65%; Cochran's Q test $P<.01$) for patients with pulmonary embolism with syncope versus those with pulmonary embolism without syncope and a weighted risk difference of 6% (95% CI 1% to 10%). I^2 and Cochran's Q test P values indicated considerable statistical heterogeneity. Because the interpretation of these tests is hampered by the presence of large studies,[50] we performed a sensitivity analysis with the omission of the 4 largest studies.[28-31] In this analysis, I^2 decreased to 35%, with a nonsignificant P value and similar results (OR 1.95; 95% CI 1.31 to 2.91).

We extracted data on the presence of hemodynamic instability from 17 studies.[7,25-33,36-40,42,47] Hemodynamic instability was present in 17% (95% CI 16% to 18%) of patients with syncope (1,315/7,592) compared with 17% (95% CI 17% to 18%) of those without syncope (51,477/293,891). Patients with pulmonary embolism and syncope have a statistically significant higher odds of hemodynamic instability compared with those without syncope (pooled OR 4.36; 95% CI 2.27 to 8.37; I^2 93%), corresponding to an absolute risk difference of 12%, indicating a higher risk of hemodynamic instability in patients with syncope (95% CI 7% to 18%) (Figure 2*C* and *D*). As we did in the previous analysis, we performed a sensitivity analysis with the omission of the study by Keller et al.[28] Patients with pulmonary embolism and syncope had a higher odds of hemodynamic instability compared with those with pulmonary embolism without syncope (OR 4.87; 95% CI 3.93 to 6.04), corresponding to a risk difference of 15% (95% CI 9% to 22%). When we omitted studies in which hemodynamic instability was considered according to the presence of hypotension only (n=5),[27,34,37,42,47] we obtained similar results (pooled OR 4.71; 95% CI 2.13 to 10.42; risk difference 22% [95% CI 11% to 33%]). Comparable results, but without statistical heterogeneity (I^2 0%; nonsignificant P value), were found in a sensitivity analysis with the omission of 4 large studies (OR 5.14; 95% CI 3.91 to 6.76).[28-31]

Two studies differentiated between patients without syncope and those with presyncope.[29,35] A higher short-term mortality was observed in patients with pulmonary embolism and presyncope or syncope compared with those with pulmonary embolism without syncope (pooled OR 11.04; 95% CI 8.25 to 14.77; I^2 0%). Also, patients with

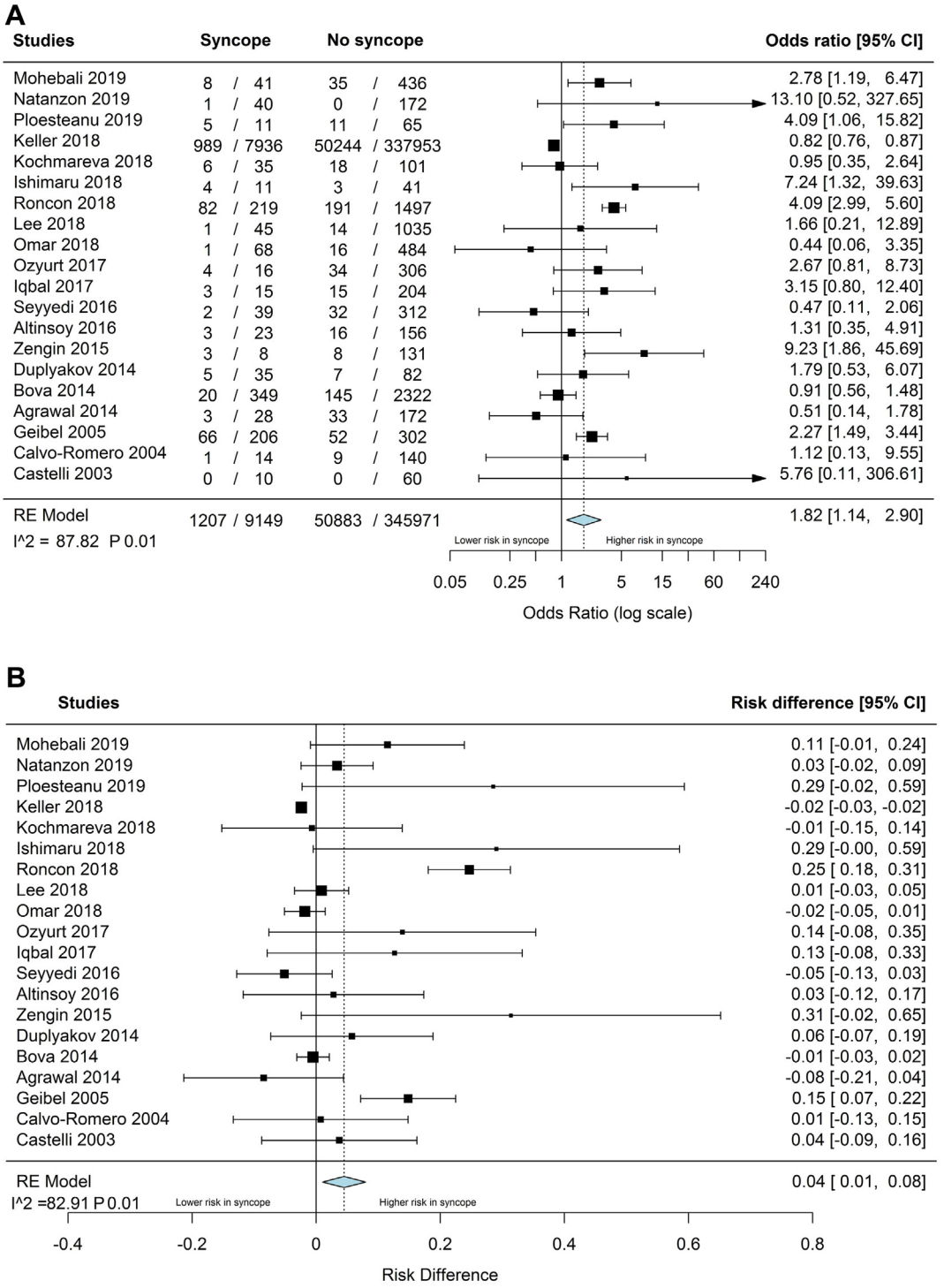
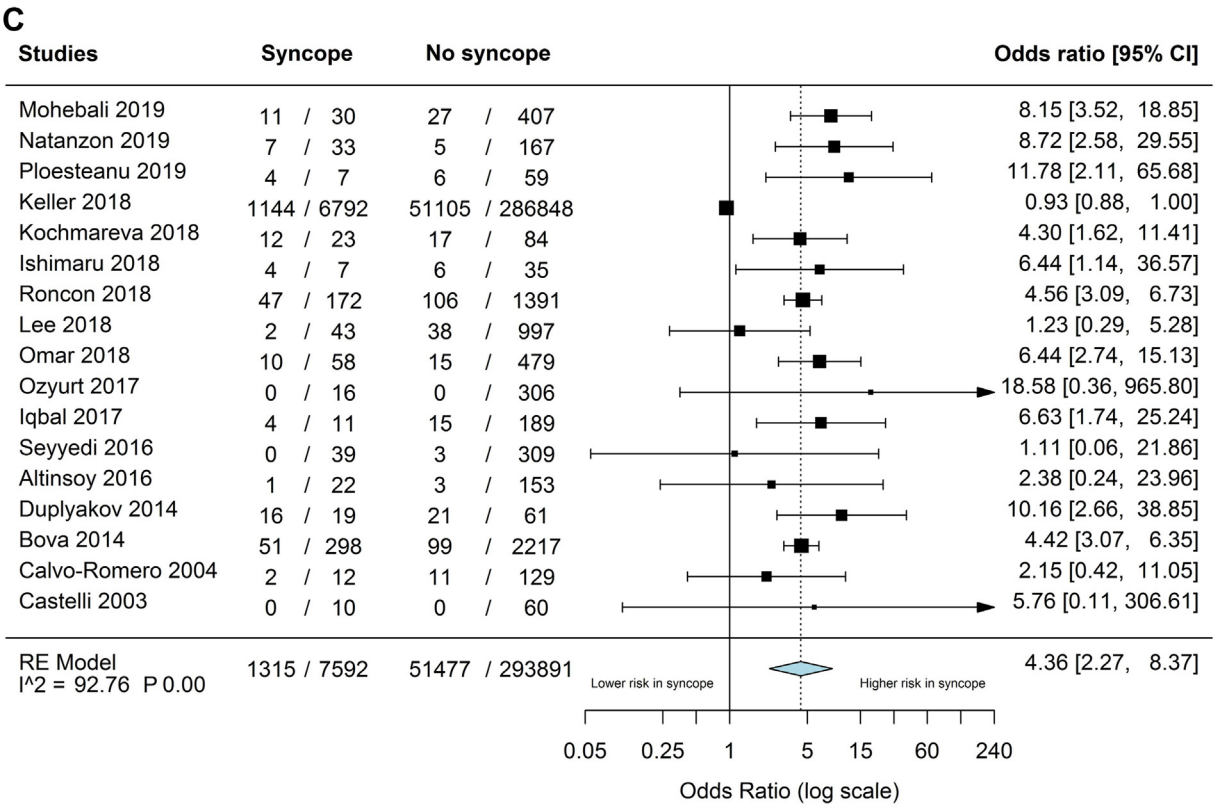


Figure 2. Forest plots illustrating OR and risk difference for primary and secondary outcomes in patients with pulmonary embolism with syncope at presentation compared with patients with pulmonary embolism without syncope. The included studies are ordered by year of publication. We decided to order studies chronologically to assess whether increased attention for the association between syncope and adverse outcomes may have influenced clinical management.[55] *A*, Forest plot illustrating OR for short-term mortality in patients with pulmonary embolism with syncope at presentation compared with patients with pulmonary embolism without syncope. *B*, Forest plot illustrating risk difference for short-term mortality in patients with pulmonary embolism with syncope at presentation compared with patients with pulmonary embolism without syncope. *C*, Forest plot illustrating OR for hemodynamic instability with pulmonary embolism with syncope at presentation compared with patients with pulmonary embolism without syncope. *D*, Forest plot illustrating risk difference for hemodynamic instability with pulmonary embolism with syncope at presentation compared with patients with pulmonary embolism without syncope.



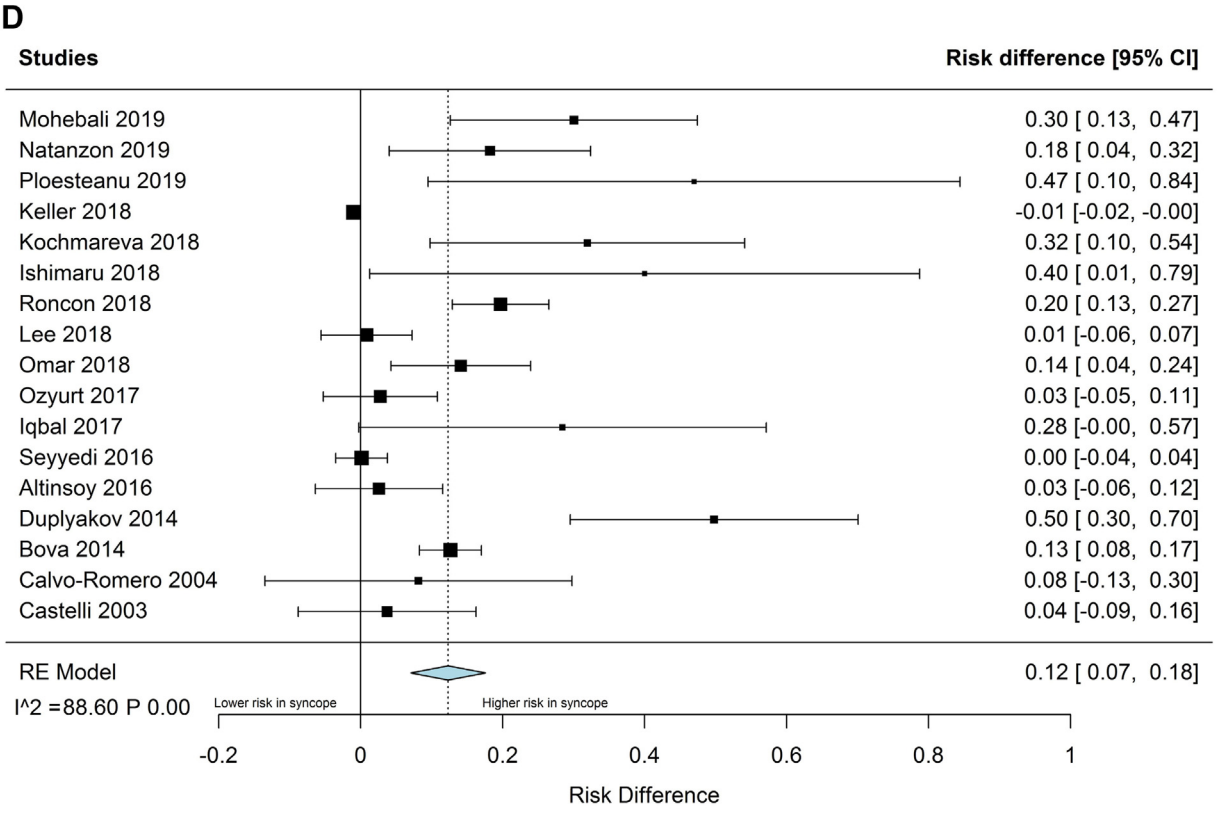


Figure 2. Continued

Table 2. Sensitivity analysis for the association between syncope and short-term mortality.

Subgroup	No. of Studies	Pooled OR* (95% CI)
30-day mortality	10	2.23 (1.34–3.72)
Inhospital mortality	10	1.15 (0.71–1.87)
Prospective studies	7	1.36 (0.68–2.70)
Retrospective studies	13	2.23 (1.23–4.05)
Studies on prognostic value of syncope	14	1.87 (0.98–3.57)
Studies with other main objective	6	1.68 (0.84–3.36)
Omitting studies with risk of bias score within the upper quartile	16	1.91 (1.23–2.97)
Studies with risk of bias score within the lowest quartile	7	1.92 (0.82–4.52)
Studies with proper definition of syncope	11	2.38 (1.37–4.13)
Omitting studies with high risk of bias in regard to study participation	16	1.47 (0.97–2.23)
Omitting studies with high risk of bias in regard to study participation and without proper definition of syncope	12	1.98 (1.09–3.62)
ED population only	5	1.60 (0.96–2.67)
Hospitalized patients only	15	3.17 (0.97–10.41)
Prevalence of syncope <10%	7	1.66 (0.99–2.80)
Prevalence of syncope ≥10%	13	2.15 (0.98–4.75)
Mean or median age <60 y	3	2.08 (1.25–3.47)
Mean or median age ≥60 y	17	0.83 (0.33–2.08)

*OR greater than 1 indicates higher short-term mortality in patients with pulmonary embolism and syncope versus patients with pulmonary embolism without syncope.

presyncope or syncope were more often hemodynamically unstable (pooled OR 3.25; 95% CI 2.34 to 4.53; I^2 0%).

Sensitivity Analyses

Table 2 shows the results of prespecified sensitivity analyses for the association between syncope and short-term mortality in patients with pulmonary embolism. When studies with a high risk of bias in regard to those domains that are most relevant to this research were eliminated (ie, study participation and prognostic factor measurement), the association remained significant (OR 1.98; 95% CI 1.09 to 3.62), as it did when studies with a high overall risk of bias were omitted (ie, risk of bias score as described in the "Materials and Methods" within the upper quartile), and with studies using a proper definition of syncope only (ie, in correspondence with current guidelines[5]). However, a higher OR indicating higher mortality in patients with pulmonary embolism with syncope was found for 30-day mortality and retrospective studies, whereas a nonsignificant positive trend was observed for inhospital mortality and prospective studies. To explore clinical heterogeneity, we performed additional sensitivity analysis comparing studies involving an emergency department (ED) population or hospitalized patients only, a less than 10% versus greater than or equal to 10% prevalence of syncope, and mean or median age younger than 60 years and 60 years or older. With the exception of studies with a mean or median age of 60 years or older, the direction and magnitude of the association were similar across these subgroup analyses (Table 2).

To explore whether the higher odds of mortality for patients with pulmonary embolism and syncope could be explained by hemodynamic instability or other patient characteristics, meta-regression was performed. Figure 3*A* illustrates the results of univariate meta-regression analysis with OR for mortality as outcome. Circles represent the individual studies, their size being inversely proportional to the variance of the estimated treatment effect. The straight meta-regression line illustrates a 0.05-unit increase in OR for mortality for patients with pulmonary embolism and syncope versus those with pulmonary embolism without syncope for every percentage-point increase in difference between proportion of hemodynamically unstable patients (95% CI 0.01 to 0.09; P=.05), although CIs did not reach statistical significance in the case of a small difference in hemodynamic instability (dotted lines). These findings indicate that the higher odds of mortality in patients with syncope are largely explained by a higher proportion of patients with hemodynamic instability. Other univariate analyses showed that larger difference in standardized mean age (Figure 3*B*) or proportion of patients with thrombolytic therapy, malignancy, or cardiac disease (data not shown) was not associated with OR for mortality for patients with

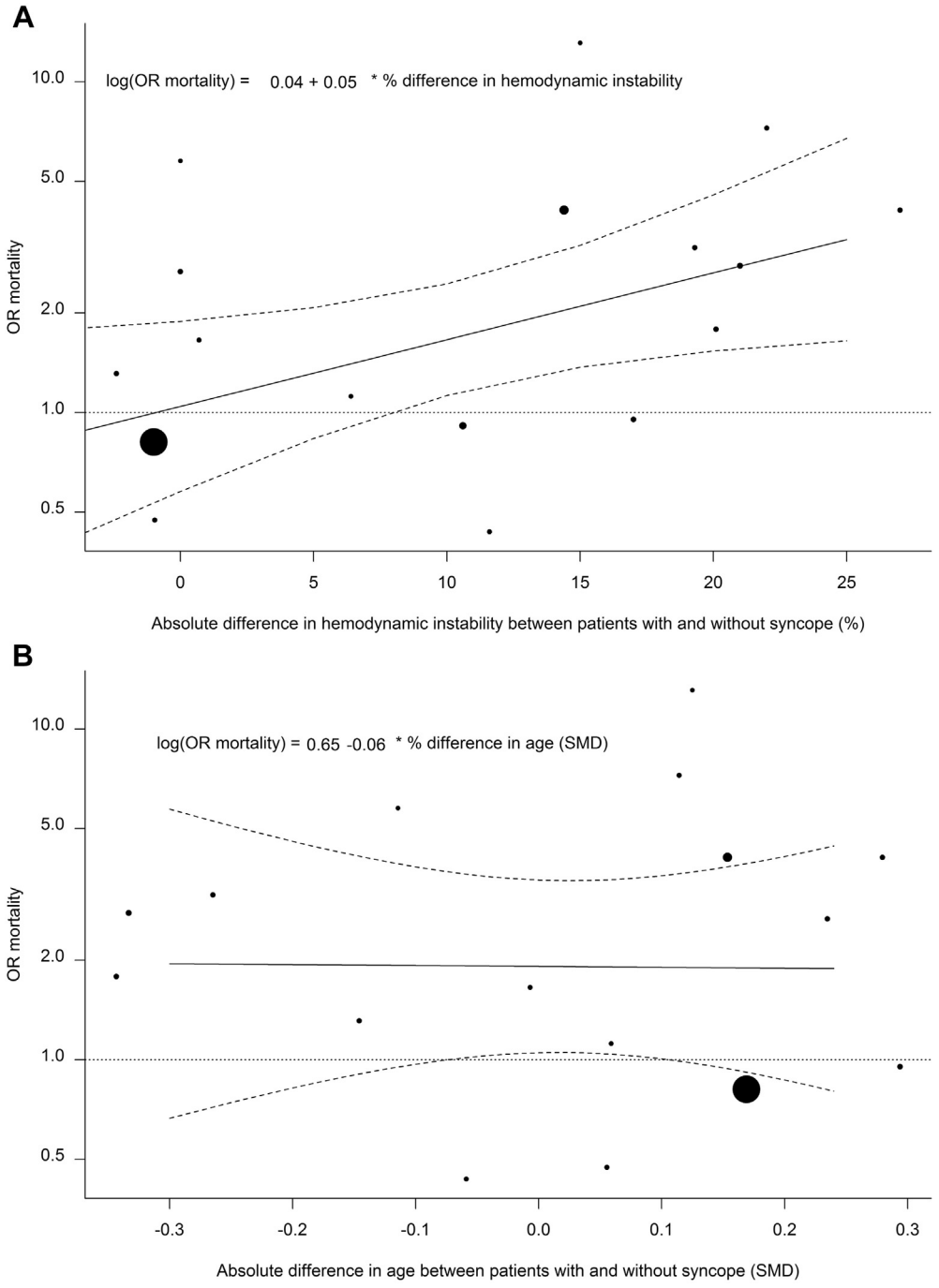


Figure 3. Univariate meta-regression analyses with short-term mortality as outcome. The straight line represents the meta-regression line. This illustrates the increase in OR of mortality for an increase in difference between proportion of hemodynamically unstable patients in those with and without syncope. Dotted lines represents lower bound and upper bound of the 95% CI. Circles represent the individual studies, their size being inversely proportional to the variance of the estimated treatment effect. OR greater than 1 indicates higher short-term mortality in patients with pulmonary embolism and syncope versus those with pulmonary embolism without syncope. *A*, Univariate meta-regression with difference in hemodynamic instability as independent variable. *B*, Univariate meta-regression with standardized mean difference in age as independent variable. *SMD*, standardized mean difference.

pulmonary embolism with syncope versus those with pulmonary embolism without syncope.

Overall, risk of bias was low because the majority of studies were judged to be at low risk in most QUIPS domains (Figure 4). However, studies scored less favorably in regard to confounding and prognostic factor measurement. In 50% of the studies, information on potential confounders (thrombolytic therapy, heart disease, malignancy, and age) was insufficient. In addition, 9 studies scored as high risk of bias on prognostic factor measurement because the authors did not provide a definition of syncope[25,32,37,39,41-44,48] or used *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* and discharge codes of syncope, which may have led to incomplete data.[28] Risk of reporting bias was considered to be low because results of the individual studies corresponded well with what was reported in the methods sections. Prepublished study protocols were available only for prospective studies focusing on pulmonary embolism risk assessment in general, and did not mention syncope in particular.[41,42,45,49,51] Publication bias was considered unlikely because the funnel plot for mortality showed reasonable symmetry (Figure 5), which is affirmed by Egger's test *P* values of .44.

LIMITATIONS

Our analyses have limitations. First, it is unclear to what extent the presence of syncope may have played a role in risk classification by treating physicians. The definition of syncope was heterogeneous across studies and possibly across cases because the presence of syncope was assessed by individual physicians. Similarly, the definition of hemodynamic instability differed across studies, and different cutoff points for hypotension were used. Therefore, misclassification bias may have influenced the observed associations. In addition, recall bias may be present because in some cases syncope will have occurred before patient arrival at the hospital.

Although the large number of patients included in the meta-analysis allowed reasonable effect estimates, data on potentially relevant confounders were available only in some studies (malignancy, cardiac disease, and thrombolytic therapy) or not at all (respiratory disease, hemodynamic parameters, and antihypertensive medication). Thus, we were limited in our meta-regression analyses. Additionally, risk of bias in especially the largest individual studies must be taken into account. Adjusting for hemodynamic instability in individual studies would have been stronger evidence than meta-regression because the latter may be subject to aggregation bias and ecologic fallacy. Caution is warranted with patients who sustained head injury during the syncopal event, which increases risk of intracranial bleeding. It is unclear to what extent this may have played a role in the present study because neither intracranial bleeding nor head trauma was mentioned in the included studies. Nonetheless, the associations we found in our main analysis are physiologically plausible because mechanisms underlying syncope in pulmonary embolism are associated with short-term mortality, hemodynamic instability, and older age.[8,52-54]

DISCUSSION

In patients with acute pulmonary embolism, syncope is associated with a 4% (95% CI 1% to 8%) higher short-term mortality (OR 1.82; 95% CI 1.14 to 2.90) and a 12% (95% CI 7% to 18%) higher prevalence of hemodynamic instability (OR 4.36; 95% CI 2.27 to 8.37). The higher short-term mortality is explained by differences in hemodynamic instability. Although significant statistical heterogeneity was present, our results are consistent with pathophysiologic mechanisms underlying syncope in pulmonary embolism.[52-54]

With the addition of multiple large, recently published articles and meta-regression analysis, our study adds important information to what is known from a previous meta-analysis by Barco et al.[15] This meta-analysis included 29 articles comprising 21,956 patients with pulmonary embolism (n=3,706 with syncope); a proportion, but not all, of the included articles overlap because of differences in eligibility criteria.[33-37,41,42,47,49] The pooled OR for short-term mortality of 1.73 (95% CI 1.22 to 2.47) and OR for hemodynamic instability of 3.50 (95% CI 2.67 to 4.58) for patients with pulmonary embolism and syncope versus those with pulmonary embolism without syncope are in line with our results. Barco et al[15] suggested that the higher mortality depends on either a difference in hemodynamic instability or bias in the included studies. We found a positive association between syncope and mortality in patients with pulmonary embolism, which remained significant when we omitted studies considered to be at high risk of bias. This makes the second explanation less likely. Our meta-regression analysis confirms the association between syncope and mortality in patients with pulmonary embolism through hemodynamic instability.

The study by Keller et al[28] comprised 97% of patients included in this meta-analysis. The prevalence of syncope among patients with pulmonary embolism in their study population was remarkably lower compared with that in

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement: mortality	Outcome measurement: risk classification	Confounding	Statistical analysis and reporting
Studies on prognostic value of syncope in patients with PE							
Mohebali 2019	−	+	−	+	+	+	+
Natanzon 2019	+	+	?	+	+	+	+
Ploesteanu 2019	+	+	+	+	+	?	+
Keller 2018	+	+	−	+	−	+	+
Roncon 2018	−	+	+	+	+	?	+
Lee 2018	+	+	+	+	+	+	+
Omar 2018	+	+	+	+	+	?	+
Ozyurt 2017	+	+	−	+	+	?	+
Iqbal 2017	+	+	+	?	?	?	+
Seyyedi 2016	+	+	+	+	+	?	+
Keller 2016	+	+	+	+	+	?	+
Altinsoy 2016	+	+	+	?	?	+	+
Duplyakov 2014	+	+	+	+	+	+	?
Calvo-Romero 2004	+	+	−	+	?	+	+
Castelli 2003	+	+	?	+	?	+	+
Studies on risk assessment or predictors of prognosis in PE with data available on syncope and mortality							
Kochmareva 2018	?	+	−	+	+	+	+
Ishimaru 2018	+	?	+	+	+	+	+
Hobohm 2016	+	+	−	+	+	?	+
Zengin 2015	?	+	−	?	?	?	?
Bova 2014	+	+	−	+*	?	+	+
Agrawal 2014	+	+	−	+	?	?	?
Geibel 2005	+	+	−	+	+	?	+
Duplicate or overlapping patient population							
Jenab 2015	+	+	?	+	?	?	+
Jiménez 2014	+	+	−	+*	+	+	+
Lankeit 2012	+	+	−	+*	+	?	+
Konstantinides 1997	+	+	−	+	+	?	+

Figure 4. Quality assessment of the included studies, according to the QUIPS tool.

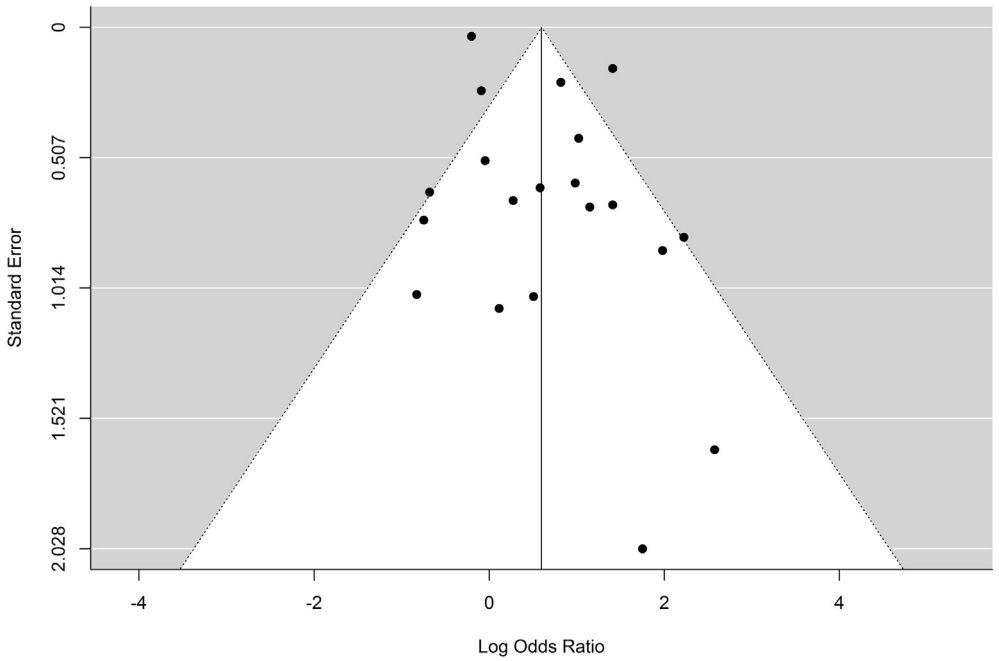


Figure 5. Funnel plot showing the log OR for mortality in patients with syncope versus those without it on the horizontal axis against corresponding standard errors on the vertical axis.

the other included studies (2% versus 13%). This is presumably related to underreporting because *ICD-10* codes and discharge diagnoses were used to define syncope. In case of urgent symptoms or comorbidities (eg, cardiac arrest), it is unlikely that syncope is registered as the diagnosis. This may explain the significantly lower mortality in all patients with pulmonary embolism and syncope. Alternatively, it may insinuate that patients with syncope are more closely monitored so that hemodynamic deterioration is detected sooner. This is supported by the finding of Roncon et al[29] that, compared with patients with presyncope, those with syncope more often received thrombolysis and had a lower 30-day mortality.

In hemodynamically unstable patients, syncope likely reflects hypotension caused by right ventricular dysfunction and diminished left ventricular filling.[52-54] Hemodynamic status is currently the cornerstone of risk stratification in pulmonary embolism because hemodynamic instability is associated with a high risk of mortality.[8,19] The absence of an association between syncope and short-term mortality when restricting to studies with a mean or median age of 60 years or older suggests effect modification by age. However, univariate meta-regression analyses showed otherwise. Our results underline the importance of risk stratification by hemodynamic status in the elderly as well as in younger patients as a first step in clinical management of pulmonary embolism. Subsequently, in hemodynamically stable patients, guidelines recommend further risk stratification using risk scores to decide whether home treatment may be appropriate. Hypotension is already part of the Pulmonary Embolism Severity Index, its simplified version, and the Hestia criteria.[12-14] Therefore, syncope would not be a valuable addition to these scores. However, this concerns only clinical management in regard to pulmonary embolism. Whether hospitalization is required to investigate possible other underlying causes or for consequences of syncope (eg, head trauma) should be decided on a case-by-case basis.

In summary, syncope in patients with acute pulmonary embolism is associated with a higher short-term mortality and higher odds of hemodynamic instability. The association between syncope and short-term mortality in patients with pulmonary embolism is explained by a difference in hemodynamic instability. This emphasizes the importance of monitoring hemodynamic status and value of current risk-stratification scores in pulmonary embolism with and without syncope.

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